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10/066,074	01/31/2002	Lloyd Mervyn Davis	D5453-00096	2489

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EXAMINER	
FORMAN, BETTY J	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 04/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,074	DAVIS, LLOYD MERVYN	
	Examiner	Art Unit	
	BJ Forman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☒ Claim(s) *3,5-8,15 and 16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12 October 2004 has been entered.

Status of the Claims

2. This action is in response to papers filed 12 October 2004 in which Claims 1 and 14 were amended. All of the amendments have been thoroughly reviewed and entered.

The amendments incorporate the limitations of Claims 3, 5-8 and 15-16.

The previous rejections in the Office Action dated 15 March 2004 are maintained. Applicant's arguments have been thoroughly reviewed and are discussed below. New grounds for rejection are discussed.

Claims 1-16 are under prosecution.

Claim Objections

3, Claims 3, 5-8 and 15-16 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Independent Claim 1 has been amended to incorporate the limitations of Claims 3, 5-8 and 15-16, but these claims have not been canceled. Therefore, these claims fail to further limit Claim 1.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-8 and 14-16 rejected under 35 U.S.C. 102(e) as being anticipated by Kuhr et al (U.S. Patent No. 6,294,392, filed 21 July 1999).

Regarding Claim 1, Kuhr et al discloses a method for detecting molecules that have participated in a chemical reaction and that have become temporarily supported at the site of reagent (Abstract) the method comprising providing a flow cell (Capillary) providing within the flow cell a solid support having a surface, supporting at least one reagent molecule to the surface (Example 1, Column 22, lines 53-62) introducing at least two flowing solutions in to the flow cell wherein at least one solution comprises a labeled molecule (target DNA w/oxidizable sugar backbone and amine containing base, Abstract, lines 16-18) and at least one solution comprises a buffer with no detectable label. The method steps include introducing the solution having the labeled molecule for hybridization and then switching solutions to introduce the buffer to remove non-specific hybrids wherein the two solutions are

at different locations at any time (Column 23, lines 6-33), providing a detector and "substantially" simultaneously to switching solutions, also switching the location of a reagent (un-hybridized target) causing the target to move through the detection zone and detecting the signal emitted and repeating to detect a series of reactions (Example 1, Column 23, line 50-Column 14, line 6 and Column 25, line 17-Column 26, line 33) wherein the concentration of the labeled molecule is greater than 10^{-8} M (Column 25, line 55). Kuhr et al further teach their method includes a light source and detecting emitted light (Column 18, lines 41-43).

Regarding Claim 2, Kuhr et al disclose the method detects a single molecule (Column 26, lines 13-15).

Regarding Claim 3, Kuhr et al disclose the method detects molecules that have participated in the reaction e.g. that have hybridized (Example 1).

Regarding Claim 4, Kuhr et al disclose the method wherein a single reaction is detected by detecting a single molecule (Column 26, lines 13-15).

Regarding Claim 5-8, Kuhr et al disclose the method wherein the concentration of the labeled molecule is greater than 10^{-5} M (Column 25, line 55).

Regarding Claim 14, Kuhr et al disclose the method wherein an array of supported reagents is used and detection is separately accomplished for each reagent of the array (Column 25, line 1-Column 26, line 15).

Regarding Claim 15, Kuhr et al disclose the method wherein the steps are repeated (Example 1).

Regarding Claim 16, Kuhr et al disclose the method wherein time between reactions is controlled by time between repetitions i.e. each zone of DNA is detected (following denaturing)as it moves past the detector (Column 23, lines 58-60).

6. Claims 1-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Williams (U.S. Patent No. 6,255,083, filed13 December 1999).

Regarding Claim 1, Williams discloses a method for detecting labeled molecules that have participated in a chemical reaction and that have become temporarily supported at the site of reagent (i.e. polymerase in the presence of primer hybridized to immobilized template wherein both the polymerase and primer are temporarily supported, Column 13, lines 40-60) the method comprising providing a flow cell, providing within the flow cell a solid support having a surface, supporting at least one reagent molecule to the surface introducing at least two flowing solutions in to the flow cell wherein at least one solution comprises a labeled molecule and at least one solution comprises a buffer wherein the two solutions are at different locations at any time i.e. the solution containing the label is introduced followed by the wash solution to remove unbound label directing the flowing solutions with respect to the supported reagents to immerse the supported reagent in the solution comprising buffer, providing a light source and a detector, substantially simultaneously with step f) switching the detector (i.e. scan with the scanner) to cause the labeled molecule to pass through the illumination zone and detecting light emitted at the illumination zone (Column 2, line 17-Column 3, line 10 and Example 2, Column 14, line 61-Column 15, line 26).

Regarding Claim 2, Williams discloses the method wherein a single labeled molecule is detected by the step of detecting light emitted from the illumination zone (Example 2, Column 14, line 61-Column 15, line 26).

Regarding Claim 3, Williams discloses the method wherein a chemical reaction is detected by detecting the presence of labeled molecules that have participated in the reaction i.e. labeled nucleotides (Column 2, line 17-Column 3, line 10).

Regarding Claim 4, Williams discloses the method wherein a single chemical reaction is detected by detecting the presence of a single labeled molecules that has participated in the

reaction by detecting light emitted from the illumination zone (Example 2, Column 14, line 61-Column 15, line 26).

Regarding Claims 5-8, Williams discloses the method wherein the concentration of the labeled molecules is above 10^{-5}M (Example 4, Column 17, lines 49-51).

Regarding Claim 9, Williams discloses the method wherein the label is fluorescent (Example 2, Column 15, lines 5-15).

Regarding Claim 10, Williams discloses the method wherein the supported reagent comprises a supported polymerase and a nucleic acid and the solution of labeled molecules comprises at least one fluorescently labeled NTP with no quenching moiety (Fig. 4, Column 13, lines 40-49 and Examples 1-2, Column 14, line 22-Column 15, line 15).

Regarding Claim 11, Williams discloses the method wherein fluorescent labels are attached to the gamma phosphate of the NTP (Column 2, lines 37-40).

Regarding Claim 12, Williams discloses the method wherein two or more distinguishable labels are used to label two or more different types of molecules i.e. a different label for each type of nucleotide (Column 2, lines 37-40 and Example 2, Column 14, line 62-Column 15, line 15).

Regarding Claim 13, Williams discloses the method wherein optical detection includes identifying labels by their property e.g. excitation light, emission light and location of detection (Column 15, lines 5-15).

Regarding Claim 14, Williams discloses the method wherein an array of supported reagents and optical detections are separately accomplished for each reagent (Column 4, lines 47-50 and Column 15, lines 5-15).

Regarding Claim 15, Williams discloses the method of claim 3 wherein a series of reactions is detected by repeating the method steps of Claim 1 (Example 2, Column 14, line 62-Column 15, line 26).

Response to Arguments

7. Applicant states that the claims, as amended overcome the above rejection. However, Applicant provides no specific arguments regarding the teaching of Williams. Because the amendments merely incorporate the limitations of previously rejected Claims 3, 5-8 and 15-16 into Claim 1, the amendments do not alter the scope of the rejected claims. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quake et al (U.S. Patent Application Publication No. 2002/0025529 A1 which is a divisional of 09/707,737 filed 6 November 2000) in view of Williams (U.S. Patent No. 6,255,083, filed 13 December 1999).

Regarding Claim 1, Quake et al disclose a method for detecting labeled molecules that have participated in a chemical reaction and that have become temporarily supported at the site of reagent (i.e. polymerase in the presence of primer hybridized to immobilized template wherein both the polymerase and primer are temporarily supported, ¶ 176-181) the method comprising providing a flow cell, providing within the flow cell a solid support having a surface, supporting at least one reagent molecule to the surface (¶ 148) introducing at least two flowing

solutions in to the flow cell wherein at least one solution comprises a labeled molecule and at least one solution comprises a buffer (¶ 177-178) wherein the two solutions are at different locations at any time i.e. the solution containing the label is introduce followed by the wash solution to remove unbound label (¶ 11 ¶ 178 and Claim 5) directing the flowing solutions with respect to the supported reagents to immerse the supported reagent in the solution comprising buffer, providing a light source and a detector, substantially simultaneously with step f) switching the detector (i.e. scan with the scanner) to cause the labeled molecule to pass through the illumination zone and detecting light emitted at the illumination zone (¶ 201-206) wherein a series of reactions is detected by repeating the method steps of Claim 1 (¶ 9-11) and wherein the time interval between successive reactions is controlled by controlling time between successive repetitions (¶ 223-229).

Quake et al is silent regarding the concentration of the labeled molecules. However, labeled molecule concentrations above 10^{-8}M were well known and routinely practiced in the art at the time the claimed invention was made as taught by Williams (Example 4, Column 17, lines 43-58). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the labeled molecule concentration of Quake et al to obtain concentrations above 10^{-8}M as instantly claimed. One of ordinary skill in the art would have been motivated to utilized routine experimentation to thereby derive the instantly claimed concentrations for the expected benefits of optimizing labeled molecule concentrations and maximizing experimental conditions.

It is noted that *In re Aller,* 220 F.2d 454,456, 105 USPQ 233,235 states where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum by routine experimentation.

Regarding Claim 2, Quake et al disclose the method wherein a single labeled molecule is detected by the step of detecting light emitted from the illumination zone (¶ 199).

Regarding Claim 3, Quake et al disclose the method wherein a chemical reaction is detected by detecting the presence of labeled molecules that have participated in the reaction i.e. labeled nucleotides (¶ 178, 193 and 199).

Regarding Claim 4, Quake et al disclose the method wherein a single chemical reaction is detected by detecting the presence of a single labeled molecule (i.e. labeled nucleotide) that has participated in the reaction by detecting light emitted from the illumination zone (¶ 178, 193, 199 and 218).

Regarding Claim 9, Quake et al disclose the method wherein the label is fluorescent (¶ 181-182).

Regarding Claim 10, Quake et al disclose the method wherein the supported reagent comprises a supported nucleic acid and a polymerase and the solution of labeled molecules comprises at least one fluorescently labeled NTP with no quenching moiety (¶ 178, 181 and 191).

Regarding Claim 11, Quake et al disclose the method wherein fluorescent labels are attached to the beta or gamma phosphate of the NTP i.e. pyrophosphate (containing the beta and gamma phosphates) is detected to detect NTP incorporation (¶ 212).

Regarding Claim 12, Quake et al disclose the method wherein two or more distinguishable labels are used to label two or more different types of molecules i.e. a different label for each type of nucleotide (¶ 181).

Regarding Claim 13, Quake et al disclose the method wherein optical detection includes identifying labels by their property e.g. excitation light, emission light, fluorescent lifetime and location of detection (¶ 199 and 202-204).

Regarding Claim 14, Quake et al disclose the method wherein an array of supported reagents (i.e. two-dimensional substrate with localized positions) and optical detections are separately accomplished for each reagent (¶ 47, 132 and 204).

Regarding Claim 15, Quake et al disclose the method of claim 3 wherein a series of reactions is detected by repeating the method steps of Claim 1 (¶ 9-11).

Regarding Claim 16, Quake et al disclose the method wherein the time interval between successive reactions is controlled by controlling time between successive repetitions (¶ 223-229).

Response to Arguments

10. Applicant states that Quake does not teach synchronization of the read out signal with the introduction of the wash solution i.e. detection being substantially simultaneously".

The argument has been considered but is not found persuasive. The courts have stated that claims must be given their broadest reasonable interpretation consistent with the specification *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969); and *In re Zletz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (see MPEP 2111). The claimed "substantially simultaneously" is given the broadest reasonable interpretation consistent with the broad claim language and specification wherein "substantially simultaneously" is not defined. Substantially is a relative term that broadens the temporal meaning of simultaneously such that the claimed detection and wash are not required to be simultaneous, but instead within some other broader and undefined time frame.

Quake specifically teaches their method wherein "the template is washed to remove any unincorporated label and the presence of any incorporated label is determined" (¶ 178). This embodiment wherein the washing and detecting are taught within a single sentence clearly teaches "substantially simultaneously" washing and detecting. Quake provides further examples of "substantially simultaneously" washing and detecting wherein label incorporation is detected "in the wash stream" (¶ 212). Furthermore, Quake teaches that their method "increases the speed" of analysis by reducing time for exchanging reagents and between different steps which clearly suggests "substantially simultaneously" washing and detecting as

claimed. Hence, given the broadest reasonable interpretation of the claimed "substantially simultaneously" washing and detecting in view of the embodiment of Quake wherein the step of washing and detecting are taught within a single sentence, Quake teaches the broadly claimed "substantially simultaneously" washing and detecting.

Furthermore, the claims are written so as to encompass numerous embodiments other than synchronized washing and detecting. For example "switching at least one of said light source, detector, or location of said at least one reagent molecule" encompasses a variety of functions. Switching a light source encompasses, turning it off, turning it on, moving it, using a different light source, changing a filter in the light and etc. Because the claims are so broadly written, they are broadly interpreted thereby encompassing a range of functions beyond the asserted synchronization. Hence, the claims read on the prior art.

11. Claims 1-8, 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramsey et al (U.S. Patent No. 6,376,181, filed 28 April 1997) in view of Williams (U.S. Patent No. 6,255,083, filed 13 December 1999).

Regarding Claim 1, Ramsey et al disclose a method for detecting labeled molecules that have participated in a chemical reaction and that have become temporarily supported at the site of reagent the method comprising providing a flow cell (Fig. 1-3), providing within the flow cell a solid support having a surface and supporting at least one reagent molecule to the surface introducing at least two flowing solutions in to the flow cell wherein at least one solution comprises a labeled molecule (ds-DNA specific dye) and at least one solution comprises a buffer (wash) wherein the two solutions are at different locations at any time i.e. the solution containing the label is introduced followed by the wash solution to remove

unbound label directing the flowing solutions with respect to the supported reagents to immerse the supported reagent in the solution comprising buffer, providing a light source and a detector, substantially simultaneously with step f) switching the detector to cause the labeled molecule to pass through the illumination zone and detecting light emitted at the illumination zone (Column 5, line 2-61 and Example 3, Column 6, line 53-Column 7, line 6).

Ramsey et al is silent regarding the concentration of the dye molecule. However, labeled molecule concentrations above 10^{-8}M were well known and routinely practiced in the art at the time the claimed invention was made as taught by Williams (Example 4, Column 17, lines 43-58). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the labeled molecule concentration of Ramsey et al to obtain concentrations above 10^{-8}M as instantly claimed. One of ordinary skill in the art would have been motivated to utilized routine experimentation to thereby derive the instantly claimed concentrations for the expected benefits of optimizing labeled molecule concentrations and maximizing experimental conditions.

It is noted that *In re Aller*, 220 F.2d 454,456, 105 USPQ 233,235 states where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum by routine experimentation.

Regarding Claim 2, Ramsey et al disclose the method wherein a single labeled molecule is detected by the step of detecting light emitted from the illumination zone (Example 3, Column 6, line 53-Column 7, line 6).

Regarding Claim 3, Ramsey et al disclose the method wherein a chemical reaction is detected by detecting the presence of labeled molecules that have participated in the reaction i.e. labeled nucleotides Example 3, Column 6, line 53-Column 7, line 6).

Regarding Claim 4, Ramsey et al the method wherein a single chemical reaction is detected by detecting the presence of a single labeled molecules that has participated in the

reaction by detecting light emitted from the illumination zone (Example 3, Column 6, line 53-Column 7, line 6).

Regarding Claims 5-8, Williams discloses the method wherein the concentration of the labeled molecules is above 10^{-5}M (Example 4, Column 17, lines 49-51).

Regarding Claim 9, Ramsey et al disclose the method wherein the label is fluorescent (Example 3, Column 6, line 53-Column 7, line 6).

Regarding Claim 13, Ramsey et al disclose the method wherein optical detection includes identifying labels location of detection (Example 3, Column 6, line 53-Column 7, line 6).

Regarding Claim 14, Ramsey et al disclose the method wherein an array of supported reagents and optical detections are separately accomplished for each reagent Example 3, Column 6, line 53-Column 7, line 6).

Regarding Claim 15, Ramsey et al disclose the method of claim 3 wherein a series of reactions is detected by repeating the method steps of Claim 1 (Example 3, Column 6, line 53-Column 7, line 6).

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (571) 272-0741. The examiner can normally be reached on 6:00 TO 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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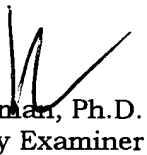

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Art Unit: 1634
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